UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

In Re: Levaquin Products Liability Litigation,	File No. 08-md-1943 (JRT/AJB)
	Minneapolis, Minnesota October 6, 2010 2:00 P.M.

BEFORE THE **HONORABLE JOHN R. TUNHEIM**
UNITED STATES DISTRICT COURT JUDGE
(**MOTIONS HEARING**)

APPEARANCES

For the Plaintiffs: **RONALD S. GOLDSER, ESQ.**
LEWIS J. SAUL, ESQ.
ROBERT BINSTOCK, ESQ.
KEVIN FITZGERALD, ESQ.
MICHAEL LONDON, ESQ.

For the Defendants: **JOHN DAMES, ESQ.**
WILLIAM H. ROBINSON, JR., ESQ.
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Proceedings recorded by mechanical stenography; transcript produced by computer.

2:00 P.M.

(In open court.)

THE COURT: You may be seated. Good afternoon, everyone. We're ready to proceed today. This is civil case MDL number 08-1943, and the individual Schedin case is 08-5743, overall In Re: Levaquin Products Liability Litigation.

Counsel, plaintiffs first, note your appearances.

MR. GOLDSER: Good afternoon, Your Honor. Ron Goldser for plaintiffs, and while I have the floor, I would like to introduce to you Michael London. Mr. London is the co-liaison co-lead counsel of the New Jersey Levaquin litigation, and he has made a special trip to join us today.

THE COURT: Very well. Welcome.

MR. LONDON: Thank you, Judge. Good afternoon.

THE COURT: I hope you're not a Yankees fan.

MR. LONDON: I can truthfully say a Mets fan.

THE COURT: Well, then, I am sorry.

MR. LONDON: So are we.

MR. SAUL: Good afternoon, Your Honor. Lewis Saul for the plaintiffs.

MR. BINSTOCK: Your Honor, Bob Binstock for the plaintiffs.

MR. FITZGERALD: Good afternoon, Your Honor.

Kevin Fitzgerald for the plaintiffs.

THE COURT: Good afternoon to all of you.

MR. DAMES: Good afternoon, Your Honor. John Dames for the defendants, and I, too, would like the chance to introduce John Winter seated behind me, Your Honor.

THE COURT: Mr. Winter.

MR. WINTER: Good afternoon, Your Honor.

MR. ROBINSON: Good afternoon, Your Honor. Bill Robinson for the defendants.

MS. VAN STEENBURGH: Tracy Van Steenburgh for the defendants, Your Honor.

MR. ESSIG: Good afternoon, Your Honor. Bill Essig for the defendants.

MR. O'SHAUGHNESSEY: John O'Shaughnessey for the defendants.

THE COURT: Good afternoon to all of you. We have quite a number of motions today. Let's see. I think five plaintiffs' motions and four defense *Daubert* motions and then the motion regarding confidential designations.

Okay. Mr. Goldser?

MR. GOLDSER: Your Honor, we've had some conversation between the parties. Also present in the courtroom is Ms. Beth Hawkins. She was here the last time at the last hearing on punitive damages. She is with Bloomberg News, and in light of her presence today and in

light of the issue that we had last time with confidential documents and the likelihood that we will talk about confidential documents again today, I thought it appropriate to take up the confidentiality motion first.

I think we can do that quickly. From there, we have agreed that the next motion will be the Seeger/Layde *Daubert* motions brought by plaintiffs. After that, we will take up the combined Smith and Zizic *Daubert* motions, which is a defense motion.

We also discussed the possibility of submitting several of the motions on the pleadings. That would be the Rodricks motion, the Zhanel motion and the intent and motive, corporate motive motion. So we're inclined to do that unless we somehow have gobs of extra time that we don't know what to do with.

I thought, although we didn't talk about it, I thought after Smith and Layde since the only ones that would be remaining are Holmes and Waymack, we would take them in that order, Holmes and then Waymack, so we conclude the day with Waymack. I know our side is prepared to go into tomorrow. It wasn't clear to me whether the Court had intended to go into tomorrow if we didn't conclude today.

THE COURT: The Court has scheduled interviews tomorrow morning for choosing a new magistrate judge, which wasn't anticipated before. I had the morning held, and

that takes all of the morning. And I've got trial in my current trial schedule tomorrow afternoon, so I think right now I don't have time tomorrow.

If we needed more time, we will put it back on the calendar just as quickly as we can.

MR. GOLDSER: Okay. The confidential motion is defendants' motion. It's their burden, so I presume they would go first on the motion.

THE COURT: Okay. Very well.

Ms. Van Steenburgh.

MS. VAN STEENBURGH: Thank you, Your Honor. May it please the Court. I think that the issue of the confidentiality has been fairly well briefed, Your Honor, and I was just going to make three points today with respect to that motion.

The first of which is to remind the Court of the context and how we got here procedurally. There was a stipulated protective order that the parties entered into in 2007 pursuant to Rule 26(c), and it was agreed upon, and the terms were agreed upon. The kinds of materials that were confidential were parsed out in the agreement.

Three years went by, and the plaintiffs then brought a motion to amend to add punitive damages, and it is some of the exhibits that are attached to that motion and the actual memorandum itself that the plaintiffs seek

public disclosure of.

They have never said anything within the three years during the period that they have reviewed and used the documents about challenging the confidentiality. It's only in the context of a motion to amend, and this goes to the issue of open access, public interest that the plaintiffs have raised as part of their response to the motion.

But it's important that this has been raised in the context of a nondispositive motion where the plaintiffs have put forth evidence, and as Mr. Goldser reminded the Court several times, defendants are not allowed to provide any evidence and the Court cannot consider any evidence. And now the plaintiffs want to release that information on the grounds that gee, public access is, it's an open court system. The public has an interest.

The cases that really talk about judicial openness and open courts and releasing briefs and documents are often in the context of a dispositive motion where each side has an opportunity to fully brief and use exhibits. If you look at Judge Frank's *CMI* decision, you will see that he looked at that very issue.

It was a summary judgment motion in which that was decided, and even in the context of a summary judgment motion, there were pages and pages of documents that Judge

Frank still withheld pursuant to the protective order.

So there is a context in which we need to put this, and it is not just access is absolute and for all purposes, which then brings us back to the actual protective order in this case. There is a presumption when you enter into these that there is good cause for keeping certain documents confidential.

And the plaintiffs here have challenged us with respect to 61 of the documents, and defendants have, we believe, provided good cause to the Court within three categories that we put together. If in fact the Court would prefer an individualized document by document review of each of the documents, we are happy to do that.

THE COURT: I think dividing them into three categories made sense to the Court.

MS. VAN STEENBURGH: Okay.

THE COURT: If there is any particular document that is exceptional in one way or the other, you're certainly free to raise it.

MS. VAN STEENBURGH: All right. And we did go through on pages 6 through 10 the reasons under each of those categories why there was good cause, and frankly, the plaintiffs nibble at the margins but really do not attack any of those reasons and just attack on a few grounds.

For example, they argue that the documents are

stale. They don't provide specifics as to documents. Maybe the marketing documents are stale, but as the Court in the *Brookdale* case, and I think the Court here can understand, many marketing documents would be interesting documents to competitors, and those documents remain confidential.

There are other documents, for example, documents having to do with discussions relative to an indication that J & J was looking to seek from the FDA regarding Levaquin that they didn't pursue. Competitors would be very interested to see what that discussion was and what those indications were.

So even though those discussions happened many years ago, the fact that they happened many years ago does not necessarily make them nonconfidential or that there isn't good cause to keep them confidential again. Similarly, as the Court probably knows from some of the other briefing, there is a licensing agreement that J & J has with Daichi, and there are obligations, contractual obligations and other marketing partner obligations that the company honors in terms of the information that is gathered and shared among marketing partners.

And thus, that information, too, is confidential and should remain so because those relationships continue up to this day. It's not as though those relationships

have gone away.

The plaintiffs argue, well, you know, none of the stuff is a trade secret, but that's not the criteria by which good cause is to be judged here. There are specific categories within the protective order that the plaintiffs agreed on and now want to renege on and say well, really you need to show that it was a trade secret.

We don't think that that is the standard by which the good cause should be judged. They also argue that well, we can get some of these documents under a FOIA request, and that may be true, but the criteria for a FOIA request and what may be confidential based upon our competitive interest could be very different.

In fact some of those FOIA or the MCA documents were redacted, so there is even a recognition by some of the regulatory authorities that there is confidential information. In fact, one of the documents itself was marked confidential by a regulatory authority in recognition that there was some confidential research and development information.

One of the things that the Court, we believe the Court should look at, and the Eighth Circuit has said this, is what is the hardship on the defendants? There is the potential for competitive harm in terms of research and development, commercial interests, but what is the hardship

to the plaintiffs. Here there is none, Your Honor.

They have had access to the documents. They can continue to use the documents. There is no harm to the plaintiffs. The only harm that they're claiming here, and this is where they are trying to claim that there is a compelling interest that would somehow surpass the need for confidentiality, is some kind of public health interest.

And frankly, we believe that's a ruse. That is, there is nothing to the public health argument. What they say in their brief is, if these documents and the brief are released, this will spur more thoughtful discussion between prescribers and patients. Yet some of the documents include lists of vendors that were used for things or a business plan or who was going to have responsibility as between the marketing partners for certain research.

None of those documents are going to spur conversations between patients and physicians. The public, they say too much about the public health interest here. There is some claim also that people are liable to die. We're not aware of any cases of wrongful death in the MDL claimed as a result of Levaquin.

And again, the public health interest, as I indicated before, there are some documents talking about another indication that hasn't been necessarily approved or they didn't pursue with the FDA, how that would spur

conversations between patients and their physicians is unknown.

The public health claim is not a compelling interest here. There is a compelling interest by defendants to maintain certain confidentiality, and we have been very careful to go through those documents, release the ones -- there were even a few where literature was marked because it was on top of an e-mail.

The literature comes off because of course that is not confidential, but we have been very careful to mark those documents and maintain the confidentiality of the documents that are business, proprietary, trade secret, commercial, research and development, all of those categories that remain under the protective order.

Thank you, Your Honor.

THE COURT: Thank you, Ms. Van Steenburgh.

Mr. Goldser?

MR. GOLDSER: Thank you, Your Honor. I think Ms. Van Steenburgh misplaces the burden of proof on this motion. The original protective order was entered into for the convenience of the parties to facilitate the discovery in this case.

The protective order specifically makes clear that if there is a demand by plaintiff for the removal of confidentiality, the burden is on the defendant to show

that confidentiality applies. There is no presumption of good cause anywhere. The order specifically takes that presumption, if any exists in the law, away.

The burden is defendants' to show that there is good cause and that the harm to them is, outweighs any benefit to the public health, but several things about this motion just completely perplex me. Ms. Van Steenburgh starts talking about the notion of, this is a one-way motion and only plaintiffs' documents are going to be disclosed.

Well, I invite the defendant to withdraw the confidentiality designation of the five million or so documents that they have designated confidential throughout the course of this litigation. If they want to make their case in the public, they're more than welcome to make their case in the public.

We have only sought the D designation of 115 documents of which defendant now contests, I think some, I think the number is 65. They have withdrawn their designation of confidentiality of half of the documents that we have already talked about.

The ones they still claim are confidential in many respects are quite curious. For example, actually the ones that they have withdrawn their confidentiality claims on make their argument disingenuous and internally

inconsistent, for example. All of plaintiffs' expert reports, Martin Wells, Martyn Smith, Tom Zizic, Cheryl Blume, a number of the depositions that we cited, Carl DeStefanis, George Zhanel, their expert, Daniel Fife, their internal epidemiologist who by the way they are not planning to call to trial, James Kahn, Dr. Waymack, their expert epidemiologist, Dr. Seeger, all of those deposition transcripts, all of those reports have not been included as confidential.

And every last one of those contains substantial citations to documents, either by citation or by quotation. So we have depositions where confidential documents are used that have not been designated as confidential or where the confidentiality is waived. We have documents that were used last week in court where this Court allowed some of those documents to be opened up.

There will be documents that are going to be used in trial, which will be a public trial and open to everybody to see, to see those documents. I rather would be surprised if this Court excluded from the trial Ms. Hawkins or anybody else from the public.

We have so many of these documents used in expert reports. We have --

THE COURT: What do you need the documents for now at this time, Mr. Goldser?

MR. GOLDSER: The reason this comes up now, Your Honor, is we have reached the stage where we have been able to cull down the documents and identify from our perspective the documents that are important.

The last step in the analysis, if you reach it because you have found that the defendant has made a showing of good cause, that they have made a showing of specific, serious and clearly defined injury, only then do you get the question of balancing what it is that plaintiffs intended to use the documents for.

Last week on September 30th, the CEO of Johnson & Johnson appeared before Congress in response to the issue of a number of the recalls that Johnson & Johnson has experienced in the last year. There were two in particular that were being discussed that day, the recall of Motrin -- retrieval and recall of Motrin products and the recall of the Children's Tylenol.

And Mr. Weldon, the Johnson & Johnson CEO, says things like, it is essential that we work closely with Congress, the FDA and others to restore the public's confidence in McNeil consumer healthcare products. He says, it is critical that the public have accurate information about what transpired at McNeil and how we came to have a string of product recalls.

Not only might there be a public discussion of

issues of this kind, Your Honor, there are public discussions of issues of this kind, and they are pending in front of Congress at this very time.

And so while we talked in our brief about the fact that there are many patients out there who have taken Levaquin and who will continue to take Levaquin and who have never ever before heard the notion that Levaquin has greater tendon toxicity than any of the other fluoroquinolones, that was what we cited in our brief.

But then we realized that Mr. Weldon made these statements in front of Congress, and we would love to let Congress see what is going on in this litigation at the same time that they are evaluating all of the other recall issues.

So it's important to patients. It's important to doctors that they see some of this information, and apparently, it's important to Congress. We don't think this Court should keep this information from those people.

Thank you very much.

THE COURT: Ms. Van Steenburgh?

MS. VAN STEENBURGH: A couple of things, Your Honor, in response to Mr. Goldser. First of all, there is no misplacement of the burden of proof. We have the burden of proof. That's true. We believe that we have shown good cause, and in fact the plaintiffs, if you look at their

memo, really do not take after any of the reasons that we have explained.

There has been good cause shown, and as again, the plaintiffs nibble around the edges but really never get to that good cause.

THE COURT: Mr. Weldon's testimony, does that change the ball game here?

MS. VAN STEENBURGH: No, it shouldn't change the ball game here. This is not -- again for a couple of reasons. One, in terms of the posture of where this is, Mr. Goldser said this is a one-way motion. This is not a one-way motion. This is about judicial access, open access to the Court.

They have collected and culled certain documents and now want to make those documents public. It is not appropriate to say, well, then why don't you just release five million documents, and we'll just make all of this public to the Court.

This is not something that is subject to a congressional inquiry. This is not something that someone has taken to a congressman. There has been no indication here at all that anyone has taken this to Congress or this rises to some kind of inquiry that Congress would want to know. That is a red herring. That is something that has been used by plaintiffs based upon information in the

newspaper.

Second of all, with respect to the deposition transcripts, all the deposition transcripts are not included wholesale as part of the exhibits. So Mr. Goldser is saying that all of these transcripts were included as part of the exhibits isn't true. There are limited transcripts.

And with respect to the expert reports, we have consistently filed those expert reports, if we used them as part of a motion, under seal if they contained information about confidential documents. So we have maintained consistency with respect to those.

Mr. Goldser's comment about trial? There is a provision in the stipulated protective order, I believe it is paragraph 10, that talks about the Court employing a mechanism, if necessary, to keep some of these documents confidential at trial. It isn't that anybody has waived it and we're going to open this up at trial.

THE COURT: What do you anticipate at trial? Say several of these documents, if they're still subject to the protective order, need to be used either by you or by the plaintiffs. What are you anticipating?

MS. VAN STEENBURGH: One of the things that I have thought about, what we are going to try to do is cull down with the plaintiff to see if there are any joint

exhibits, so if there are joint exhibits and any of them are confidential documents, we would have to establish a procedure that we would try to work out with the plaintiffs for keeping those confidential.

Either those would be confidential during testimony and there would be no one in the courtroom at that time, or we could work out some other mechanism. If there are other documents that are going to show up on plaintiffs' list to which we object and those are admitted and there is testimony about those, we will have a mechanism in place, again try to work something out with the plaintiffs prior, but we will certainly consult with the Court on that.

Finally, I do have to say that in response to your question, why is it they need these documents now? Mr. Goldser said that they culled down the documents to just a few documents. We just got their trial exhibit list. It's 1423 documents. Culling it down, apparently, from five million I suppose down to 1423 is a lot, but there are a lot of documents.

It is not really a question of culling down the documents, and these are the ones that they need access to, and these are the ones that need to be publicly disclosed. We maintain that we have shown good cause, Your Honor, and in fact that the confidentiality should remain.

THE COURT: Thank you, Ms. Van Steenburgh.

One question for you, Mr. Goldser: Is there any specific issue that is contained in these documents, whether it's 61 or 65, I'm not sure, that patients and doctors aren't aware of right now with all the publicity that has surrounded this case and these types of drugs?

Is there anything specific that is in there that there is no public notice of?

MR. GOLDSER: There are two issues that come immediately to mind. One I already mentioned, and that is the question of whether or not levofloxacin has greater tendon toxicity than the other fluoroquinolones.

Johnson & Johnson to this day denies that, and they set up the Ingenix study in order to allegedly prove that fact. The medical literature that exists on the subject, some of it is published but in very obscure journals, and much of it is not published and is internal.

So doctors to this day don't know that if they have a choice between prescribing for a respiratory patient Levaquin versus Avelox that they need to prescribe Avelox because --

THE COURT: Isn't that an issue that we're going to address at trial?

MR. GOLDSER: Whether or not that's true?

THE COURT: Yeah.

MR. GOLDSER: Why isn't it the case that doctors have the right to know what the medical literature is regardless of what happens at this trial? Why don't they get to know that?

The other thing that doctors need to know as the Ingenix study is touted is how that Ingenix study came about, both its genesis, why it was done and perhaps more importantly, how it was done. And it's our position it was done poorly and nonscientifically.

And to the extent that our witnesses have strongly held opinions that other doctors would be interested in knowing about, about whether this study is valid or not valid, we think that's important to be known in the scientific community.

Those are the two immediate responses that I come up with in answer to your question.

THE COURT: Ms. Van Steenburgh?

MS. VAN STEENBURGH: I am just a little perplexed. What I heard Mr. Goldser say was, just as you said, Your Honor, I have the same question as to whether it has greater tendon toxicity, the issue at trial.

But he said that some of the studies are published in obscure journals. Well, I am not sure that it is -- I guess those doctors have access to the journals that they want to subscribe to, and they can do their own

research. It isn't an obligation of ours to tell them what they need to look at.

Second of all, I think the Court was suggesting that there is information out there. There is a black box right now, and a black box is put in a certain place so that a doctor can talk with his or her patient if he wants to in terms of what is on the label with respect to that.

The other thing that is a little perplexing is Mr. Goldser said, well, our witnesses want to be able to talk about how the Ingenix study came about. I don't know what he has in mind, whether his experts are going to go visit with doctors and explain all of this or what is going to happen.

That doesn't really translate into, disclosure of the documents turns into something that physicians need to know, especially if witnesses are going out there and calling on physicians.

Thank you, Your Honor.

THE COURT: Anything else, Mr. Goldser?

MR. GOLDSER: No. We will submit on the record, Your Honor.

THE COURT: Okay. Well, on this one, I'm going to grant defendants' motion to protect these remaining documents. I don't see at this stage so close to the trial in this case a compelling reason to release the remaining

confidential documents. I think at least by category the defense has demonstrated a continuing reason for protection.

I think any and all of them, of course, are subject to re-designation during the course of the litigation, and in particular, if there are any of these documents that are to be used at trial, I think we should focus in on the particular documents at the time to determine how best to treat them.

And the Court's preference, of course, is to make sure that they're public, but I don't see a reason at this stage for release of these documents. The plaintiffs' lawyers have full access to them, and it seems that they are being designated as trial exhibits.

And when we get down to the basics for the trial, I think that's the time where we need to zero in on some of these documents, and some of them may well be released publicly at that point in time.

Let's go on to the motions.

MR. GOLDSER: The first motion that will be presented, Your Honor, will be on Dr. Seeger and Dr. Layde, and if you would just give me a second to set this up for Mr. Saul.

For some reason I don't get it up on my screen here. Of course today is the day that it doesn't work.

THE COURT: Okay. Are we set? Very well.

Mr. Saul.

MR. SAUL: Thank you, Your Honor. May it please the Court. Lewis Saul, S as in Sam a-u-l, on behalf of plaintiffs. This motion is brought on behalf of plaintiffs to exclude in whole the testimony of Dr. Seeger.

Dr. Seeger is the lead author of a study by, his study is entitled Achilles Tendon Rupture and Its Association with Fluoroquinolone Antibiotic and Other Potential Risk Factors in Managed Care Population. We move the Court to exclude Dr. Seeger's testimony because it does not meet the standards of *Daubert versus Merrell Dow Pharm, Inc.*

The standards that are enunciated in *Daubert*, I would like to pass out my slide presentation, if I might, Your Honor. As the Court knows -- well, let me regress a bit. A week or two ago, we argued a motion for punitive damages, and we explained to the Court what the Ingenix study was and why it was performed in plaintiffs' view.

To refresh the Court's memory, around 2001, there were regulatory questions in Europe concerning Levaquin and tendon toxicity. Johnson & Johnson while having no interest in Europe, selling no Levaquin in Europe, went to its trading partner Aventis, who sold Levaquin in Europe, and said we will take over the study.

The sole reason for taking over the study was to protect its market in the United States. The study that they conducted was intentionally designed to reach a result that they, that they wanted to reach. In fact 16 studies before it had found a -- that there was an increased, that there were increased tendon disorders with ofloxacin and levofloxacin.

This is the only study that has ever found that there is not an increased risk. The *Daubert* criteria, it's slide one, are, there are four criteria: Whether the expert's theory can be tested objectively? It cannot. Whether it has been subject to peer review and publication? It has not. The existence and maintenance of standards and control? There were none. Whether the scientific evidence offered has been generally accepted in the scientific community? It has not.

For each and every one of these particular criteria, Dr. Seeger's study, Ingenix, going forward, the Ingenix study, it does not meet the minimum standards for scientific authenticity.

THE COURT: Let me ask you a question, Mr. Saul: At trial in this case or in the Schedin case, do you intend to introduce or discuss the Ingenix study at all?

MR. SAUL: We do, Your Honor. We're simply moving today to exclude the study -- Dr. Seeger's testimony

regarding the issue. We intend to use it for all other purposes to show that they did a study for marketing purposes, that they did it in order to control the market and that it was done for purposes other than which it was designed.

THE COURT: But wouldn't Dr. Seeger be the only person who can really testify as to why things were done as they were, illuminate the study, which would be part of the evidence?

MR. SAUL: Your Honor, I probably shouldn't be saying this, but if you said to me today, if either the whole study goes in or you're not referring to it, I'll take the whole study. We will have to parse out the scientific aspects as compared to why the study was done and the reason therefor and why it is a basis for our punitive damage claim and it actually is the basis for, it's the center of our claim.

THE COURT: Mr. Seeger was the designer of the study, correct?

MR. SAUL: He, Dr. Seeger, Daniel Fife who is the lead of epidemiology at Johnson & Johnson and Alec walker, Dr. Seeger's mentor and higher up at Ingenix, they were the architects of the study.

THE COURT: And then was he also then the, for lack of a better term, the chief scientific person on the

study?

MR. SAUL: He was, Your Honor.

THE COURT: Go ahead.

MR. SAUL: As I go through this, I'm going to talk about each of those three people that we just mentioned. I'll try to be brief. I know we don't have much time, but I do want to cover all bases here.

So let me first talk about Ingenix. It is slide two of the presentation. Ingenix is an arm of UnitedHealthcare. It's here in Minnesota. It's a large healthcare insurance company. They sell insurance and they pay claims.

They have a database. They have a claims database after they pay claims. For instance, if you have a sprained wrist, they have a code for the sprained wrist, and they pay $300 for a doctor's visit. They have that database.

They perform studies on drug safety for pharmaceutical companies, including Johnson & Johnson. They regularly perform studies for Johnson & Johnson, and they receive substantial income from Johnson & Johnson. They were the developers of the Ingenix study with Johnson & Johnson, the study that we're talking about, and it was finally published in 2002.

There were three architects of this study. Alec

Walker, he was the head at Ingenix. He was the head epidemiologist. He was a person -- I'm sorry. He was a personal friend of Daniel Fife.

Daniel Fife was the director of epidemiology at Johnson & Johnson. Alec Walker was John Seeger's advisor. He was his professor, and he was his mentor at the School of Public Health at Harvard University, and he was also responsible for John Seeger being hired at Ingenix.

This is important, and I want to give the Court a frame of reference. The article was finally published in a publication called Pharmacoepidemiology and Drug Safety in 2006, so I want to talk about how these three parties were related to this particular publication because it goes to the issue of was the article peer reviewed. It was not.

From 1994 through the present, Dr. Walker was the editor and editor of Pharmacoepidemiology and Drug Safety. From 2006 to the present, he was on the board of directors of the International Society For Pharmacoepidemiology, ISPE, and ISPE is the organization which owns the publication, or it is the publication of the organization.

He was the past president of ISPE. He was the chief editor of Pharmacoepidemiology and Drug Safety, and he was coauthor of the Ingenix study.

Now, Daniel Fife was the director of epidemiology and drug safety and surveillance at Johnson & Johnson. He

is the head epidemiologist, and he was actually the architect of the study. When you asked before about what sort of documents, we had many e-mails as to how he helped create the protocol for the study.

He was a personal friend of Alec Walker's. He testified to this. He was a member of ISPE. From 2003 when the study was completed to 2006 when it finally got published, he was on the publication committee for Pharmacoepidemiology and Drug Safety. He was on the editorial board of Pharmacoepidemiology and Drug Safety, and he recommended the article be published in this particular journal.

Who is John Seeger? John Seeger is a pharmacist. I wrote here. I'm sorry. Let me go through this. I meant to say he had a PhD in epidemiology. In the slide I said pharmacology. I apologize. When he commenced work at Ingenix, this was his first epidemiological study as an employee, and it was the first study that he was a project manager for.

As I said, Alec Walker was his professor, et cetera. He was the principal investigator, as we discussed before, of the Ingenix study. What Dr. Seeger is not: He is neither a medical doctor, and he has no training or expertise in medicine or medical training. He has never seen a patient with a tendon rupture, nor has he

ever prescribed a medication. We will see how this is important.

The first criteria, the first *Daubert* criteria, can the expert theory be tested objectively? It cannot. For no other reason, I could stop my presentation now. Daniel Fife, the head of epidemiology who designed the study, stated under oath as follows on March 25th, '09:

So I think the simple answer to your question is, it would not be possible to reconstruct the data.

Their own, the head epidemiologist at Johnson & Johnson said, we cannot reconstruct the data. It's gone, and I'm going to get to how the abstraction forms were destroyed by Dr. Seeger. We discussed it during the punitive damages motion, and I will discuss it again.

Question?

THE COURT: No.

MR. SAUL: Alec Walker testified, if I wanted, if I wanted to or if I wanted to get one of my doctors to review to see if they agreed with your researchers whether or not this was the case or not, would we look at the abstraction forms, is that correct?

If it still existed.

But that's the only way we could check your work, right?

That's the only way we could check it, yes.

And if it's not there, then we couldn't check it?

That's correct.

It's not there. The algorithms, the abstraction forms, the medical records, they were all destroyed by Dr. Seeger under his tutelage. The abstraction forms, the medical records were destroyed under the tutelage of Dr. Seeger.

Approximately one month, Your Honor, after we filed the first Levaquin case in this court, the medical abstracts and medical records were destroyed under the direction of John Seeger. I will not read this to the Court. I read it during our punitive damage argument, and he takes responsibility.

The last line: Yes, it would have been -- that was -- it was my decision, and it followed one of those two scenarios -- saying the documents were destroyed.

And what month is that?

2006. It would have been October. I think it was late October. It was in the fall.

The first case in this court was filed September 15th. One month after the case was filed, all the underlying data was destroyed, gone. Dr. Seeger now, in order to determine whether someone was a case, whether they had Achilles tendon rupture, Dr. Seeger developed an algorithm.

How he developed the algorithm was, they pulled out anyone who had an Achilles tendon rupture from this billing database UnitedHealthcare. They had 1700 some potential cases. They then randomly selected 300 and, in round numbers, 350 of those cases to go and get the medical records.

There was an abstraction form that was created in which to get these medical records, and if I could, I would like to pass a copy to the Court.

THE COURT: Go ahead.

MR. SAUL: Thank you. I have passed my copy to the Court, but I am relatively familiar with it. This is about a 10 or 15 page document, and it goes through every kind of condition one could have. It goes through whether you had an Achilles tendon rupture, what kind of medication, you had, did you have these what they call covariates in them. It asks any question that they were studying.

They sent investigators out to pick 300 -- to get medical records on 350 patients. The reviewers took that abstraction form, made it out, attached certain medical records. Dr. Seeger determined in his, himself what, what healthcare providers to go and get these records. They paid $250,000 to get these abstracts done.

Dr. Seeger testified he looked at five or ten of

them and then had no use for them and didn't look at them again. First Seeger testified, and I'm going to spend a little bit of time on that, that he reviewed only a few abstract forms, and later he testified to the fact he read all of the abstraction forms. He has -- I'm going to read the testimony. It will just take a short time.

The things called the abstraction forms, you say you never looked at them, right?

Right.

Or the vast majority?

I looked at some of them, but the majority of them --

Yeah, twelve or something, under ten?

There were about 350 of them.

Something on that order.

Then he testifies later or the next day or the next day of deposition: Now you had all this information in these abstraction forms, and yet you never looked at this?

On occasion, on the few that I did look at that, I did, but no.

Next stanza: I would have noticed the fact that there was an abstraction form there, but I didn't look specifically at the abstraction form.

There is no time that you ever reviewed these

abstraction forms?

Except for those first five or ten.

So then: Who wrote this out?

This was written by me, yes.

Typed by you and everything?

Referring to abstracts.

Yes.

Okay. You wrote on here --

Oh, no. I apologize, Your Honor. At the end of the project, they -- each person that worked on the project made out a self evaluation form. Dr. Seeger made out an evaluation form. He wrote, and I was asking him here who made this out. He said he made it out himself.

On the abstraction process, and it says, he wrote this in his own hand: On the abstraction process and read all of the returned abstracts to arrive at a determination of case status. I read all of the abstractions.

That was a self evaluation.

Yes, it is.

You read all the return abstracts?

Yes.

And that's what you testified about previously in your deposition?

Yes, it is.

First he says he didn't read them. Then we get

the documents that say he acknowledged reading all of them, and then he says that's what I testified to earlier. His testimony is clearly incredible.

Now what is also interesting and very disturbing, and reluctantly I bring this up to the Court, but we -- there is evidence in the record that these abstraction forms still exist and that Johnson & Johnson has them. When we had -- when Dr. Fife was at a deposition and I was examining him, I asked Dr. Fife about what did he review in preparation for this deposition. He testified, and this is the testimony before you, Your Honor.

He testified with specificity that I reviewed the abstract forms. He testified with specificity, I did not review the medical forms. I know it was the abstract forms that I reviewed. I asked him over and over, and his testimony is clear that he said that he reviewed the abstract forms, and he was sure of it.

There was a break in the, a five-minute break because we do that every hour in a deposition. He comes back, and he says after a five-minute, well, I'm not sure. Maybe it was a medical record that I reviewed. I'm just not sure.

I asked him specifically, Dr. Fife, he's a medical doctor. Did you review a medical record? No, it was not. It was the abstraction form. He even referred to

it, what I proffered to the Court today, the abstraction form, and he said it was attached to the protocol. That's what I reviewed.

I asked Mr. Robinson for a copy of that document, and Mr. Robinson said, I don't know what you're talking about. I can't give you what I don't know what you're talking about, but there is clear evidence that Dr. Fife has or that the defendant has in their possession these abstract forms.

Noteworthy, Your Honor, is that there is one witness that they refuse to call at trial, and I've asked if they will bring him to trial because we would like to call him in our case in chief, and that's Dr. Fife. And Mr. Robinson says, we will not bring him to trial and you can't have him as a witness.

Now, back to the study and publication. One of the *Daubert* criteria, was the work subject to peer review? In the Johnson & Johnson contract with Ingenix, Ingenix was to publish the final article in five publications. They were listed. They were New England Journal of Medicine. They submitted it, rejected.

JAMA, rejected. Annals of Internal Medicine, rejected. Archives of Internal Medicine, rejected. Lancette, rejected by all. So what did they do? Dan Fife said, well, why don't you come, and we'll publish it in

the, in Pharmacoepidemiology and Drug Safety where Walker is an editor, where Fife is an editor, where Walker was the past president. It was even rejected in the first instance by Pharmacoepidemiology and Drug Safety.

Finally, it got published, and that was the only place that would accept this publication, and I suggest to the Court that that is not fair peer review. There was no peer review, and also that the reviewers knew that Alec Walker and John Seeger and Dan Fife were all authors, they testified to that, on the study.

Now, Dr. Layde is the defendants' epidemiologist, Peter Layde, who we will deal with that issue after this one. And he is their epidemiologist, so at deposition, I asked Dr. Layde that he -- strike that.

Dr. Layde at his deposition stated that the destruction of documents -- stated the destruction of documents failed to meet proper standards, and that's another *Daubert* criteria, that you have to save the underlying data so that others who read this, publish the peer reviewed study can go back and ask questions and see if it met *Daubert* standards in the scientific community.

Dr. Layde said: And my understanding is that those chart abstraction forms were not saved or not currently available at least.

My question was, Did you find that a problem?

I think that is currently not ideal epidemiological practices. That's absolutely the case. My recollection is that they said this was lost in a move, and that's, you know, unfortunate. It's not what it should have been.

Their own expert that they submitted as an expert in this case says that that's not appropriate epidemiological methodology. Now, there are standards for keeping documents. There are two that we point to here.

One is the International Society of Pharmacoepidemiology, ISPE, guidelines for archiving. To refresh the Court's recollection, ISPE is the organization that Dr. Walker was the president of. He authored these guidelines. Those guidelines say in relevant part, the archives should be maintained for at least five years after the final report or first publication of study results, whichever comes later.

Their own author said that these have to be maintained for five years, and yet they were destroyed several months after the final publication and one month after the first filing of a Levaquin case in this court.

Ingenix had their own standard operating procedure that was being passed around in 2003 that was finally effected in 2006, six months before they destroyed the documents in this case, and those were what they had to

preserve, and it even said abstraction forms, for five years after the publication.

Dr. Seeger tries to get around that by saying, oh, that only applied to studies that were commenced before the SOP. Blinding, for this fact alone that this should not be admitted into evidence. Instance report and all epidemiologists I believe agree that when an association, when an association between an exposure and an outcome is being studied, it is critical that the assessor of the outcome is blinded to exposure.

In other words, if they're studying fluoroquinolones or Levaquin and tendon rupture, the person that assesses whether the person had a rupture has to be blind. They can't know whether there is a fluoroquinolone used or an antibiotic or Levaquin.

Dr. Seeger, after much testimony and after days of testimony, admitted that he was unblinded to fluoroquinolone use. It was underlined because it was crossed out. He knew. He knew at every stage of this study what particular -- that there was a fluoroquinolone involved and which fluoroquinolone it was.

He reviewed and was aware -- the testimony from Dr. Fife, the head epidemiologist at Johnson & Johnson, I asked him, if Dr. Seeger was unblinded to fluoroquinolone use would that be a problem. At the bottom of the slide,

this was his testimony, the head and author of the article:

And it would be an error so grave that it would discount the results of the study? Talking about blinding. What does Dr. Fife say?

Yes, it would be an error so great that it would discount the results of this study. Yes, if the blind was broken and the review of these charts, these abstracts for case or noncase status was done with the exposure status known, this would be a major problem in the study.

This alone should discount --

THE COURT: Is it possible, Mr. Saul, that because of the destruction of this underlying data it may be more essential to have Mr. Seeger here to offer testimony about what was done?

MR. SAUL: Your Honor, I actually offered to the defendants that I would, because of the confusion between the science and the facts, I would withdraw my motion if they would produce in the case in chief Dr. Seeger so we could examine him in the case in chief, and they refused.

With that, if you order him to come, I withdraw my motion.

THE COURT: Go ahead.

MR. SAUL: Dr. Layde, their expert witness on blinding, he is an epidemiologist as well. Ideally that investigation should have been completely unaware of

whether a patient had been exposed to fluoroquinolones when judging whether an Achilles tendon rupture had occurred.

Quote after quote. I think you need blinding because that's something which blinding would have been preferable because that's the kind of convention in epidemiological studies. It's good practice to have blinding.

He's talking about good epidemiological. Should I continue, or have you made a decision?

THE COURT: No, I haven't made a decision because I haven't heard the other side yet so --

MR. SAUL: I tried. Excuse me.

MR. DAMES: Couple minutes again.

MR. SAUL: All right. Again, the *Daubert* criteria, there were 16 studies before this case that they all found an increased risk of -- excuse me. Sorry -- increased risk. 16 studies have found an association between fluoroquinolone exposure and an increase in the risk of tendon rupture or tendinopathy.

The Ingenix study was the only study to find that there was no increased risk of tendon rupture with exposure to fluoroquinolones. Again, it is not generally accepted in the scientific community.

To recap, Johnson & Johnson funded. The Ingenix study was fundamentally flawed. There are other issues I

need to address. The study was fundamentally flawed in a number of other ways. If you will recall, Your Honor, we discussed that the elderly were unrepresented, underrepresented. Pardon me for one minute.

As you recall at the last hearing, Your Honor, there were approximately 2 or 3 percent of Medicare patients initially included in the, in the first submission of the article to the European authorities. The European authorities said, it's underrepresented. There were about 3 percent in the study. There were 16 percent in the general population.

So they went back. They got caught. They got caught because they were supposed to be studying the elderly. They got caught. They had to go back and put them in. They had it the whole time. They could have put them in initially.

They included children. It's contraindicated in children. For this reason alone, another reason alone that Dr. Seeger should be precluded from testifying. They exclude tears. If you go, Your Honor, to the next page, it says rupture and tear. I would like to read the definition from Stedman's Medical Dictionary defining rupture as a tear.

Forcible tearing or disruption of tissue, that's a rupture. It's not a complete tear. Mayo Clinic defining

Achilles tendon rupture: If you overstretch your Achilles tendon, it can tear (rupture). The definition for a rupture includes tear.

Dr. Seeger in this study, although he called it Achilles tendon rupture and its association with fluoroquinolone antibiotics, he excluded everybody with a tear. He didn't even include them. He said those are not ruptures because, because he wanted to exclude them because -- for obvious reasons.

The next thing he did was, he excluded booting. What a boot is, there is different ways to treat an Achilles tendon rupture. You can have surgery, and you can repair it. You can cast it to repair it, or you can put what is called a cam boot. It's a big, usually blue boot with Velcro, and it keeps the leg stabilized.

As you get older, the risk of surgery becomes greater, and generally the elderly do not, they don't have surgery. They have casting or booting. Dr. Seeger did not know what a boot was. He didn't know what a cam boot was, and he was the one deciding whether or not those included in the study had a, had a rupture. He had no idea what a cam boot was.

I could read the testimony to you, but I asked him over and over. I don't know what a boot is. I don't know what a cam boot is. I don't know if it was included

in the study. I don't know what the -- he had, he had no idea what a boot was.

So this group of elderly patients, they were, the tears were excluded. The boots were excluded, and these were the elderly. There was a, there was a system to systematically exclude the group that they were attempting to study.

It appears, Your Honor, that I am done. Thank you, Your Honor.

THE COURT: Thank you, Mr. Saul.

Mr. Robinson?

MR. ROBINSON: Good afternoon, Your Honor. May it please the Court. Bill Robinson for the defendants, and I will respond to the motion to exclude in whole the testimony of Dr. Seeger.

As the Court is well aware, Dr. Seeger was the principal investigator of the Ingenix epidemiology study on Achilles tendon ruptures and fluoroquinolones and other risk factors, including -- one of the fluoroquinolones obviously was the drug at issue in this case, levofloxacin.

This was, this is, Your Honor, the only study on the subject conducted in the United States, in the United States population, and in the only healthcare database with enough subjects at the time to study what is a very rare adverse event.

The study in terms of the incidence of Achilles tendon rupture, findings were very much in conformity with other findings from other studies in Europe. The rate of Achilles tendon rupture, whether you're taking any drug or fluoroquinolone or not, is approximately one case per 10,000 person years, one case per 10,000 person years.

The Ingenix study was one of two studies that looked at the risk of Achilles tendon ruptures with fluoroquinolones, and it is the only study published or unpublished to look at the question of levofloxacin risk and Achilles tendon rupture with fluoroquinolones.

Dr. Seeger, the principal investigator of this study, holds dual PhDs in pharmacy and pharmacoepidemiology, and he is imminently well-qualified to have been the principal investigator of this study.

THE COURT: The defense is intending to call, it's Dr. Seeger, right?

MR. ROBINSON: Dr. Seeger, yes, we are, Your Honor, in our case. I would also point out, Your Honor, in terms of the testimony of Dr. Seeger, he was deposed for four days, generating over a thousand pages of testimony, and the plaintiffs have designated significant portions of his testimony to be included in their case in chief.

We don't feel it's necessary to produce him as part of their case in chief, but he will be called to

testify both as a fact witness and as an expert witness in the defense case. We will offer Dr. Seeger, Your Honor, to testify obviously about the facts of this study.

We will also offer his testimony in the area of opinions, and often the factual opinion area is not so well defined, as the Court knows, on the design of the study and why it was so designed, why was the study limited to Achilles tendon ruptures, and he can answer that question for the Court and the jury.

He will also talk about the methodologies used in the conduct of the study and why the methodologies were appropriate, scientifically accepted epidemiological principles. He will also talk about the findings and conclusions of the study following the data analysis.

The plaintiffs make continued reference to a charge that this study was somehow high-jacked from Aventis doing a study in Europe and taken over to prove a specific point with data here in the United States. Aventis was doing their own studies in Europe. Those studies were never published. The issue of that will be for another day.

One of the documents that you were shown, Your Honor, at the punitive damage hearing was a July 24, 2001, set of notes from Dr. Jim Kahn who had attended a meeting of the partners. One of the comments on that note was, we

need to do the correct epidemiology study ourselves.

So as early as July of 2001, Johnson & Johnson was looking at the possibility of doing a study for the United States population here in this country using a U. S. healthcare database.

The first protocol from Ingenix from Dr. Seeger is dated December 17, 2001. This wasn't a late development in response to something going on in Europe. It was in fact a study originated because of a perceived necessity which the Johnson & Johnson witnesses can describe to you.

The issues that the plaintiffs have raised in their motion really don't question the basic scientific methodologies that were employed here. That is, they don't question that it's totally proper to use a case control study. This was a nested case control study, to use a medical chart review to build an algorithm for final case selection and to use the database that we used.

Those are, those are basic principles of epidemiology. Those were followed here, and they are not questioned. The questions they take issue with are issues related to the factual underpinnings of this study and the way certain aspects of the study were conducted.

For example, they assert there were not enough elderly people in the population. We've responded to that in our papers. There clearly were. There were significant

number of cases over age 60 at the conclusion of the study, and the confidence intervals around the findings for the elderly were very tight, meaning strong findings.

They assert that we improperly included children in the study. Dr. Seeger's response to this is, yes, some doctors do prescribe Levaquin for children, even though it's an off label use, but why would you exclude them from a study if they're already in the database. And coincidentally, there were no cases of children who had an Achilles tendon rupture in this study, none.

They also take issue with this lack of blinding, the fact that the study was allegedly underpowered, the fact that the algorithm was perhaps improperly applied and so forth. I think, Your Honor, in order to understand the issue about the blinding and the loss of the abstraction forms, I need to talk to you a little bit about how the study was done procedurally because it is important, and the importance is, the abstraction forms were not used for the final case selection process. They were used only at a preliminary stage.

The case is a case control study. That means simply that you look for cases. Well, what are the cases? The cases you want to find under this study design are people who have an Achilles tendon rupture. You're not looking at exposure at this point to any drug, trauma or

anything else. You want to know, well, who is the case?

The way they did this in the healthcare database is, they started with a very broad definition. They used what is called an ICD code 9, International Classification of Disease code for Achilles tendon rupture, and there is a specific code for Achilles tendon rupture.

They added to that certain procedural codes, surgical procedural codes, casting codes and other kind of codes. So the initial question was, if you have -- in this database they have, they have millions, eight million people in this database or more, perhaps. You look for those codes, any of those codes. If you have any of those codes, then you drop down as a potential case.

Well, because they included casting, they had thousands, I think 20,000 or 30,000 potential cases. That's way too much to work with. What Dr. Seeger did then is, he excluded the cases that only had a casting code, nothing else. If you only had a casting code, you got excluded at this stage.

It gets put back in later as I will explain, but at this stage, you exclude the casting codes. When you do that, you wound up with a population of 1748 potential cases. Now, at this point, Dr. Seeger is ready to begin his medical records review, so he has trained medical abstractors.

And what they did is, they took a random sample, total random sample of 411 people out of the 1748. They sent these trained abstractors with this abstraction form that's been provided to you to the medical records offices, the doctors, maybe it's a surgical facility, wherever they could get the records.

The abstractors filled in the forms, brought those back, and were instructed to attach certain types of medical charts, MRI reports, things like that. Those came back to Dr. Seeger. They didn't get all 411. They got 328 of those back. So when Dr. Seeger got those back, he asked the question, did the medical facility or doctor make a diagnosis of Achilles tendon rupture in this case?

So we have 328 cases, and now he is going to look at the medical records. He testified that he looked at the first five to ten abstraction forms which were attached to the medical records and that he very clearly testified, in this stage of the process I did not need to continue to look at the abstraction forms. I had the information I needed in the medical chart itself, the medical record. So he looked at those.

Further and importantly, Dr. Seeger wasn't making a diagnosis, as is charged in the plaintiffs' papers. Dr. Seeger was simply looking to see if the doctor or medical facility, if they had made a diagnosis of Achilles

tendon rupture, and therefore, if they did, he would count that as a case. That's the process he went through.

Now, Your Honor, if -- you were provided a copy of the abstraction form by Mr. Saul. If you would turn to page 55 of that abstraction form. This is the page that is at issue in some of the questions in the case. If Your Honor will notice under the top question number five, item number G, it says fluoroquinolone use. For those patients -- strike that.

Before Dr. Seeger received these files, and when he received a file, these 328, he got the abstraction form completed and the medical record and a file folder. That's what his testimony was. Before he got those, someone would have gone through and taken out personal information and would have blacked out this item G.

If in fact, if one or more or how many ever of those 328 had used fluoroquinolones before they had a tendon rupture, that would have been redacted or blacked out. So he would have known that that person used a fluoroquinolone. He would not have known that that person, which fluoroquinolone that person used, and that's an important distinction.

As I commented earlier, Dr. Seeger said he really looked at only five or ten of these on the first pass to pick out true Achilles tendon rupture cases. Now, this is

also the document that presumably Dr. Fife talked about, and I want to make one thing perfectly clear. I don't know what Dr. Fife, what document Dr. Fife was referring to in his deposition testimony, and I made that clear on the record.

But the assertion that either Dr. Fife or the defense counsel in this case have completed abstraction forms from Dr. Seeger's study is totally not true. We never had them, and we never did have them, and I could not have shown Dr. Fife a completed abstraction form. And I made that statement on the record at the time of Dr. Fife's deposition that we did not have those abstraction forms. That's, that's on the record, and I say that to you as an officer of the Court.

If we had those abstractions forms, I would have gladly given them to the plaintiffs' counsel, and it would have probably saved everyone in this case a lot of trees in terms of paperwork on this issue. Following Dr. Seeger's review of the 328 cases, when he did his review, he found that 190 of them or 58 percent had a true diagnosis of Achilles tendon rupture.

So these were random sample cases that had been indicated by coding that they were Achilles tendon rupture cases, but when he went through them, he found only 58 percent were true Achilles tendon rupture cases. Why was

he doing this medical chart review to start with? He was doing it to find out, first of all, to select the true cases of Achilles tendon rupture.

And what was the purpose of that? The purpose of that was to use those cases, those 190 cases, to determine what is it, what are the best discriminators, what makes in the medical chart that we're going to look at with this algorithm, what makes a true Achilles tendon rupture case a case versus a case that has been misdiagnosed or ruled out case or something else.

That's why he was reviewing the medical charts. From that review, they built the algorithm, and the algorithm, I can show Your Honor a copy, but I don't want to take up too much more time here. The algorithm was used for the final case selection for the study. The algorithm is totally blinded to exposure status, meaning any use of any drug. It has absolutely nothing in it about any drug use, and it is not done by a human. It's run by a computer program.

So the cases of Achilles tendon rupture that were used to, in the final data analysis in this study were selected by this discrimination tree or algorithm totally clear of fluoroquinolone exposure and totally clear of exposure to any particular fluoroquinolone.

Now, after the algorithm does its job, that's

when the pharmacy records with the exposure come into play. At that point, Dr. Seeger gets the pharmacy records, plugs them into the data, and then you start looking at, okay, for these people who had tendon ruptures, and I will interrupt myself, Your Honor, to say, the algorithm was applied to the entire 1748 population, the original population.

When Dr. Seeger did that, he wound up with 911 cases of Achilles tendon rupture confirmed by the algorithm. He checked that, the validity of that algorithm, by taking those 328 cases that he had personally reviewed the medical charts on, and he ran those through the algorithm, and when he did that, yes, it's not perfect.

The algorithm is not perfect. It's not 100 percent, but it has a 91 percent predictability, and every epidemiologist will tell you that is an extremely high predictability. This was a very good algorithm for picking Achilles tendon rupture cases, and that's the way the cases were selected.

So the final case selection was not related in any way to this blinding of the item G number 5 on page 55. That was at a preliminary stage. The addition of the 36 elderly patients from the Medicare database brought the total case selection for purposes of the study to 947 cases. Those were compared to controls, and the data was

run, and the results were generated.

In terms of the power calculations of the study, I won't spend much time on that, but Dr. Seeger clearly testified that power calculations are done before you start a study. At the conclusion of the study, you look at the confidence intervals of your point estimates to determine how strong your study is.

If you have tight confidence intervals, you have a good strong study. If the confidence intervals are wide, you have less reliance on your point estimates, and the critical point estimates in this study, the point estimates on fluoroquinolone exposure and the point estimates on specific fluoroquinolone exposures are all very tight point estimates.

Now, the study was published in Pharmacoepidemiology and Drug Safety in 2006. Dr. Walker and Dr. Fife hold positions in that organization, and I think Dr. Walker also does hold a position on one of the boards of the organization.

Your Honor, the record is absolutely clear here that there is no evidence that any undue influence on the publication of this study was exerted by Dr. Seeger, Dr. Walker or Dr. Fife. It was rejected by some journals, and the one I recall the journal did not reject it because of any problems with the scientific methodology or the

conclusions of the study. They had a note that said, we think this is more appropriately placed in a specialty journal as opposed to a general medical journal.

In terms of the destruction by Dr. Seeger or the failure to keep by Dr. Seeger of the abstraction forms, Mr. Saul points out that the first case in this court was filed in September of 2006, and the abstraction forms were lost or not saved in the office move in October of '06. There is no testimony or indication on record or any evidence that Dr. Seeger had any knowledge whatsoever of any litigation related to this matter at that time.

The first time I contacted Dr. Seeger was in late 2008. He did not destroy these abstraction forms with any knowledge of any litigation pending. I would further point out, Your Honor, that this study was done independent of litigation in the beginning. There was no litigation pending when this study was done. Litigation was not a motive for this study in any way, shape or form.

I will conclude, Your Honor, by saying it's clear there is going to be a lot of debate about the validity of the Ingenix study and about the validity of the findings of the Ingenix study, and plaintiffs' experts have made charges along the lines you have heard here today.

Needless to say, we have responses to all those charges. The charges that are made don't go to the

methodology or credibility of the methodology of the studies. They do not rise to the level of a *Daubert* exclusion. They perhaps present jury issues on various aspects of this study in terms of the factual background for this study and whether some of the issues, like elderly people and children, would raise any questions about the findings of this study.

Those are questions for the jury. They are not matters for *Daubert* exclusion. Thank you very much, Your Honor.

THE COURT: Thank you, Mr. Robinson. Let's take a five-minute break.

THE CLERK: All rise.

(Recess taken.)

(In open court.)

THE COURT: You may be seated. Okay. What's next? We can go until about 4:45 is when we have to quit today, so what's next?

MR. SAUL: I think that Ron is going to use the Power Point this time, and I'm going to use the printed material, if I might approach.

THE COURT: You may proceed.

MR. SAUL: Thank you, Your Honor. The next motion that we have filed is a motion to exclude the

testimony of Dr. Peter Layde. Dr. Layde is an expert in epidemiology, and he is to opine about matters that we believe are beyond his area of expertise, as well as, there is no basis for him to opine upon the matters that he does.

The same criteria, *Daubert* criteria, apply equally to Dr. Layde as they did to Dr. Seeger. The third point on page one of the Power Point, I'm going to start there because I believe it's a good starting point. Dr. Layde, his testimony is essentially that there is no convincing evidence that there is an association between Levaquin and other fluoroquinolones and tendinopathies.

However, such testimony, going to page two is -- stay at page one. Such testimony is, it's that he has no basis for, for, for that opinion. That's not an opinion, that there is no convincing evidence. He doesn't say that there is an association, or he doesn't say that there is not an association.

He can't say this nebulous formula that there is no convincing evidence. It's simply not an opinion, and it's not admissible under *Daubert* because it is not an opinion. You can't cross-examine him. It's confusing to the jury, and it's simply not admissible.

Going to page three, this is where we talk about that there is no convincing evidence. Dr. Layde expresses his opinion in terms of there being no convincing evidence

that levofloxacin has an increased risk of tendon rupture compared to other fluoroquinolones. This addresses an issue that is not before the jury, whether or not the scientific evidence meets an unspecified standard.

There is no standard that he is opining about, so how can that be admissible. Testimony about undefined standards of what constitutes convincing epidemiology -- epidemiological evidence poses the risk of confusing and misleading the jury.

Page four of the Power Point, Dr. Layde's opinion that inferences that can be drawn from the studies examined were severely limited because most were conducted using administrative databases is inadmissible. He's wrong. The only study that he uses is the Ingenix study, and that used an administrative database, a building database, a database where doctors send in their diagnoses and they seek reimbursement.

He cites five or six. Going to page five, these are the studies that he says do not have, that are administrative databases and they're unreliable. He is wrong about each and every one. When questioned he said he did not know. He has never seen the databases. He has never used the databases.

He went to the web site of the databases, and he drew his opinion from that. That surely does not rise to

scientific, what is required for admissibility of scientific evidence.

The first just to run briefly through it, Van der Linden. There are medical records that were reviewed. There is medical records in the database that he used. In number 2, the Van der Linden fluoroquinolone and risk of Achilles tendon disorders, the United Kingdom MediPlus IMS Health database has medical records. It's a complete medical chart.

I'm not going to go through each one of them, but the seven studies that he cites all have used medical records, not databases. The only database that is used is the case that he relies upon. It is simply inadmissible. We covered this rather thoroughly in our brief, and I'll rely upon our brief.

The third and probably the most important part of Dr. Layde's testimony which needs to be excluded is that Layde's opinion that data on ofloxacin cannot be applied to levofloxacin is inadmissible. Dr. Layde said, just to refresh the Court's memory, this is slide number 6, that ofloxacin was the predecessor to levofloxacin.

Johnson & Johnson bought the rights to levofloxacin, which was basically a racemate, if I'm pronouncing that correctly, of ofloxacin. In other words, the molecule was reversed, and 50 percent of Levaquin is in

ofloxacin. Dr. Layde opines as an epidemiologist that you cannot use the data from ofloxacin to draw conclusions about levofloxacin. It's just simply wrong, and that will be addressed in other presentations today.

Dr. Layde is not a toxicologist. He's not a pharmacologist. He's not a biostatistician. He's not a chemist. He disclaims expertise in all of these disciplines. Yet, he opines for, if we go to the next page, yet he opines that you can use such -- you can't use such data because in some, in some molecules, the data is not transferable.

He says nothing about Levaquin. He knows nothing about Levaquin. He has never studied Levaquin. He has never looked at Levaquin. In fact, on page seven, I have a list of questions that I asked him. Did Dr. Layde know whether Levaquin was contraindicated in patients under 18? No.

Dr. Layde is considered an expert in the side effects of ofloxacin and levofloxacin but had only a vague familiarity with their adverse side effects and could not point to a single difference between them. Yet, he says you can't use one to look at the other. He can't point to a difference or something similar between the two.

He could not name a particular bacteria that ofloxacin would be used to kill. The same goes for

Levaquin. He could not name the indications for Levaquin, other than respiratory tract infections. He did not know whether levofloxacin and ofloxacin had different therapeutic effects and side effects.

But yet he is opining that you can't use one from another. He's not a toxicologist, and this is a toxicological issue, not from an epidemiologist, and it clearly should be excluded. Dr. Layde has no opinion, here is another, he has no opinion as to whether or not ofloxacin exposure causes an increased risk of tendon rupture or tendinopathy.

He has no opinion. How is he here to express an opinion when he has no opinion? That is the opinion he's going to express, that there is no conclusive evidence. I have no opinion. I just don't understand his opinion because he doesn't have one.

Back to that, the issue of ofloxacin and levofloxacin, could you use ofloxacin to define what occurs in levofloxacin. If you go to page eight, Dr. Layde says, it's not a reasonable assumption that epidemiologic data on ofloxacin can be applied to levofloxacin because many drugs that are enantiomers have different therapeutic effects and side effects from their mirror image compounds or from the racemic mixture.

So then the next thing he confuses, that that

applies that to Levaquin with no -- ofloxacin to Levaquin, with absolutely no basis whatsoever to make that opinion. That opinion must be excluded, but from plaintiffs' standpoint, we have substantial evidence that you can use the data from ofloxacin for levofloxacin.

Our experts, Dr. Smith and Dr. Zizic, document the premise with evidence ranging from published studies to defendants' own statements to the FDA in their new drug applications that you can use one for the other. I believe our brief is clear on the issues for Dr. Layde, and with that I would rest. Thank you.

THE COURT: Thank you, Mr. Saul.

Mr. Robinson?

MR. ROBINSON: May it please the Court, Your Honor. Dr. Layde is a qualified epidemiologist. He holds his degree from the Fleming School of Public Health. He has a master's, I believe, in epidemiology. His qualifications are set forth I believe in our papers.

Dr. Layde had no involvement in any of these epidemiological studies personally. We asked him to work with us as an expert witness to examine all of the studies, the published epidemiological studies on fluoroquinolones. He looked at the three published studies by the Dutch investigator Dr. Van der Linden, the two unpublished studies by Aventis and also the Ingenix study.

He will offer opinions about the methodologies used in those studies and some of the inherent problems with the methodologies used in those studies, given the particular databases and the methods that were used to search those databases. He will also offer opinions as to what conclusions can be validly drawn about the risk of tendon disorders from fluoroquinolone use and from specific drug use for each of those studies, and the same question for tendon rupture and Achilles tendon rupture.

In his report and in his testimony, he has explained his opinions and the factual basis of those opinions. Now, the plaintiffs first indicate that he should not be permitted to testify because he applied a no convincing evidence standard. He did not apply a no convincing evidence standard.

His testimony was that based on his review of the epidemiology and his education, experience and background, there was no convincing evidence of an increased risk of levofloxacin compared to other fluoroquinolones, and that opinion he held to a reasonable scientific certainty. That is the standard.

THE COURT: He's not intending to offer any legal conclusions, is he?

MR. ROBINSON: I'm sorry, Your Honor?

THE COURT: He's not intending to offer any legal

conclusions, is he?

MR. ROBINSON: No, Your Honor.

THE COURT: Okay.

MR. ROBINSON: He will offer an opinion as to his review of the studies, and we asked him the question, are any of these studies valid in predicting an increased risk of levofloxacin compared to other fluoroquinolones, and his response was, no, there is no convincing evidence of that in these studies, and that's essentially what he says in his report and in his testimony.

Now, the other point about the use, the statement about comparisons of epidemiological data on ofloxacin and levofloxacin. Of course, he is not a toxicologist or a medical doctor. He is a medical doctor, but he is not a toxicologist. He is not testifying as a toxicologist in this case. He is testifying as an epidemiologist.

His testimony is simply that from an epidemiological perspective, one cannot apply an isomer, data from a racemic like Levaquin with an L isomer and an R isomer in epidemiology studies to a drug which is only one isomer of the racemic mixture.

Now, the plaintiffs take issue with that, and they say, well, no, that's not true. You can do that from a toxicological perspective, but Dr. Layde is testifying as an epidemiologist looking at the way you conduct

epidemiology studies. These are two separate and distinct drugs. They have different therapeutic effects, and they have different side effects, and that's the way you have to look at it.

That's the basis of his statement, and he in his deposition explained the basis of that statement. So I find the challenges to Dr. Layde, quite frankly, to be just disagreements about his interpretation of the European data and a disagreement about whether one drug can be substituted for another drug in reaching epidemiological conclusions.

I don't think those are *Daubert* issues. Those are jury issues. Thank you, Your Honor.

THE COURT: Thank you, Mr. Robinson.

Yes, Mr. Saul.

MR. SAUL: Just one quick comment, Your Honor. Dr. Layde bases his entire opinion upon seven epidemiological studies, all of which he does not, he does not -- he misinterprets the databases. He bases them on that there are no medical records in these studies. It's wrong. It's in our brief.

The underlying data that he relies upon is wrong. The only other data that he relies upon is the Ingenix study, and we covered that. If that's excluded, then his opinion obviously must be excluded upon that. Thank you.

THE COURT: Thank you, Mr. Saul.

Okay. Which one is next? Defense motions?

MR. DAMES: I guess it's Dr. Smith and Dr. Zizic, Your Honor.

THE COURT: Go ahead, Mr. Dames.

MR. DAMES: Thank you, Your Honor. I think I will do this by focusing in the beginning on Dr. Smith. Some of the points that I make challenging Dr. Smith's opinions will clearly be applicable to Dr. Zizic.

Now, Dr. Smith is a toxicologist who has, whose basic opinion, the opinions that we challenge are that he believes that the, there is evidence to suggest and support that Levaquin is more tendon toxic than other fluoroquinolones.

Now, I want to clarify the standard because to some extent because in plaintiffs' responsive brief to our challenge, they suggest that the Court is required to resolve all doubts in favor of admissibility, and I just want to up front state that I believe that to be in flagrant error.

That is not the *Daubert* standard. The Court is not required to resolve all doubts in favor of admissibility, but in fact that contradicts the Court's gatekeeping function, it seems to me.

Now, there is an interesting starting point for

this analysis about the alleged increased tendon toxicity of Levaquin. We have argued at length in the course of this litigation as to the paucity of evidence that supports that proposition.

And in the testimony of both Dr. Smith and Dr. Zizic, the starting point is there is, they admit in their testimony, that it is known -- and I'm going to read what my notes are because it's startling when you think about it point by point.

There is no human study directly comparing and finding increased tendon toxicity with levofloxacin. So we start that there is no direct evidence supporting the proposition that levofloxacin is any more tendon toxic than any other fluoroquinolone. The other point that is made in the depositions of both is their conclusion, frankly, I will argue that unsupported, is that Levaquin is more tendon toxic than Cipro.

Now, the reason or the way, the method by which they get to conclude that Levaquin is more tendon toxic, even though there is no human evidence directly measuring and comparing it, is to suggest that there is animal work which supports the proposition that levofloxacin is more tendon toxin in juvenile animals and that you can predict from juvenile animals to, I assume, adult animals but certainly to human adults that those animal studies would

be directly predictive to the experience you would expect to find in humans.

Now, the Dean, frankly, I guess I'm anointing him the Dean, but probably the most significantly cited toxicologist who has studied fluoroquinolones in the world today is a man by the name of Ralph Stahlmann. His work is probably the touchstone of many of the other toxicologists' work on the toxicity of fluoroquinolones.

It is his theory, in fact, on the magnesium deficiency, which he has labeled in his papers a theory. It is that theory that has created what plaintiffs' experts, and I assume many of the researchers in the field, to be a starting point for articulating why fluoroquinolones might cause damage to tendons.

He specifically, and this is one of the articles that has been cited by both Dr. Zizic and by Dr. Smith. Dr. Stahlmann concludes, little is known about the effects of magnesium deficiency of human articular cartilage. Therefore, these forms of arthropathy in magnesium deficient humans differ from those observed in magnesium deficient rats because systematic data on the magnesium and calcium content in human joint hyaline cartilage during the period of postnatal development are lacking.

Our data in rats cannot be scaled directly to the human situation, and the extrapolation to man of the

critical development phase observed in rats is difficult. This statement about the difficulty of predicting the results of the animal data to human adults is a repetitive refrain. We have cited it from several different papers in our brief.

And it's, frankly, I think if you had to get a consensus of opinion based on the papers cited by both Dr. Smith and Dr. Zizic, there would be an agreement that we don't know the precise mechanism of action as to any fluoroquinolone toxicity in tendons. We can't explain it. We have a theory.

That theory has not been adequately tested to confirm it, and we also cannot, certainly cannot adequately explain any relative toxicity among the fluoroquinolones based on the animal work that we have done.

THE COURT: Are you arguing, Mr. Dames, that Smith and Zizic are using animal studies exclusively or as part of a larger framework of looking at various studies, the animal studies part of it is inappropriate to rely upon.

MR. DAMES: By definition that's a good question, but it is an interesting question. They rely predominantly on animal work. There are references to some anecdotal reports in the medical literature, which, quite frankly, are equally deficient in being able to detect differences

in toxicity or different rates of tendon toxicity.

Anecdotal reports don't get you there. They can't give you incidence figures. Comparing populations, they don't do that, and they cannot do it even if they purported to. They go from animal work. They also cite work done on human tendon cells, in vitro work.

So I would say a fair reading of their depositions and their opinions and their reports is that the predominant focus of their reports are the animal work. There is focus on, some focus on human tendon cell studies, and then there is additionally some examination of papers, published papers, which are in fact case reports or compilations of case reports.

So each segment by itself is too weak to sustain an opinion. I don't think the addition of those different segments adds anything to them. It only underscores, I believe, the weaknesses or the failure to measure directly any different effects in Levaquin.

I asked, and I think I asked both, about whether there was a direct head-to-head comparison anywhere between ciprofloxacin and Levaquin, and the only answer I got, and this was an answer that I received -- actually both of them had to admit this, was a study, and this was another Ralph Stahlmann study, Synergistic Effects of Dexamethasone and Quinolones on Human-Derived Tendon Cells.

Dr. Smith referred to it as the only head-to-head comparison between ciprofloxacin and levofloxacin that he knew of. The problem with this study was that it found Cipro to be more toxic than Levaquin, and I don't see how one can use the results that establish the exact opposite of your proposition as support for your proposition.

I'm not suggesting that it is evidence of the opposite, but it is certain -- because an in vitro study by itself one way or the other is not going to predict human effects, but it certainly isn't supportive of it, either. Now, one of the other articles that is an attempt to support the proposition is an article by Pouzaud. I'm probably mispronouncing the French incredibly.

This is entitled In Vitro Discrimination of Fluoroquinolones Toxicity on Tendon Cells Involvement of Oxidative Stress. Now, this was, as the title suggests, it was an in vitro study, again used as support for their propositions by both Dr. Zizic and Dr. Smith, and in this study, the conclusions again run exactly counter to those that they suggest.

The two groups, they conclude, they can differentiate the two groups of fluoroquinolones based on the results they get by exposing these tendon cells to the variety of fluoroquinolones. One is intrinsic toxicity for tendon cells that are high, and those they found with

ciprofloxacin and pefloxacin and moderate for ofloxacin and levofloxacin.

And ofloxacin they found it would be at 30 percent of something called redoc status, which I cannot explain to you on pain of death, and for levofloxacin at 22 percent. I mentioned those numbers only to show you that there are differences between levofloxacin and ofloxacin and that the lowest of the two groups was in fact levofloxacin at the 22 percent.

And it says, our study indicates that intrinsic toxicity to tendon cells varies across fluoroquinolones. It is -- they add to it in their discussion section by suggesting the following: Although in vivo and in vitro studies have investigated the potential mechanisms underlying fluoroquinolone induced tendinopathy, no reproducible model has been proposed to detect and predict intrinsic fluoroquinolone tendon toxicity.

So it is difficult to conclude based on the sum of the animal evidence, the sum of the in vitro evidence, how that supports any differences in toxicity among the fluoroquinolones, but most importantly and conclusively, how they can testify that this supports the proposition that Levaquin is more tendon toxic than Cipro, I think that failure to support that proposition is clear based on the published work that their own experts rely upon, Your

Honor.

Now, in Dr. Smith's case specifically, and I will end specifically speaking of Dr. Smith with this point: A similar opinion about relative toxicity with drugs was in -- was denied. It was excluded in the, in the recent *Baycol* opinion that was issued in August, I think, of this year.

His very analysis was excluded because animal studies do not provide a scientifically, I'm quoting, reliable basis for his opinion that *Baycol* is the most toxic statin, so this template was used before, and this template was found insufficient before. I do not know the record.

THE COURT: Wasn't the issue there that the study itself was flawed, which is slightly different than the issue of whether animal studies can be used to predict human response?

MR. DAMES: I think, Your Honor, you're correct. The study itself was flawed, but in this case, I'm not, I mean, I don't even think there is any need to criticize the studies themselves. They state what they represent, and what they represent cannot support that conclusion, but thank you, Your Honor.

THE COURT: Thank you, Mr. Dames.

Mr. Goldser?

MR. GOLDSER: Your Honor, Mr. Binstock is going to do this argument, except I'm going to preempt him for a couple minutes. You asked the question about whether there were any human studies that were involved in the testimony of Dr. Smith and Dr. Zizic, and certainly they're not relying exclusively on animal studies.

But what I've got to tell you is that Mr. Dames is operating in a completely different universe about the testimony of Dr. Smith and Dr. Zizic. What Smith and Zizic are talking about is whether on a toxicological and pharmacological level, you can compare Floxin and Levaquin. That's it.

To talk about a comparison between Levaquin and Cipro, Levaquin and moxifloxacin on a toxicological and a pharmacological level, you can do a little of that, and certainly what they've got to offer adds to the mix. But the predominant opinion, the predominant opinion and the one that matters to plaintiffs more than anything else, is can you compare Floxin with Levaquin because Johnson & Johnson had Floxin. Johnson & Johnson has Levaquin.

Johnson & Johnson had evidence that Floxin had tendon toxicity. Johnson & Johnson should have known that Levaquin was going to have similar tendon toxicity. How should they have known that? Because the animal studies tell you. What do the animal studies tell you? That

within rats, the comparison between Floxin and Levaquin on a tendon rupture, a cartilage arthropathy and C-max area under the curve, t-halflife, all of those toxicology measures were very similar between each other.

The same was true of dogs. The same was true of monkeys. What do we know about humans? We don't know from a toxicological level because you're not ethically allowed to perform those experiments to see whether you submit a human being to one or the other and see if they have tendon ruptures. That's not ethical. So you can't do those studies.

But what we do know about humans because these studies were done and they are part of the NDA that was submitted in 1995 or so, toxicologically Floxin and Levaquin are the same. The C-max is within one standard deviation, and Dr. Zhanel said there is no statistical difference. The area under the curve is the same. No statistical difference.

There are charts that can show this, and so Smith and Zizic say, I've got animals. I've got rats. I've got dogs. I have got monkeys. I have got humans. Floxin and Levaquin, they all look alike; therefore, I can say that because they all look alike at all these toxicological levels, they all look alike because the rats and the dogs and the monkeys look alike on tendons and cartilage between

each other, it is likely at least for purposes of doing a warning that they will look alike with regard to Levaquin.

And so you've got animal studies. You've got human studies. You've got the combination of the bunch, and within the confines of your decision in *St. Jude* and Judge Schiltz's decision in the *Polski* case which was the Zicam, Cold-Eeze zinc problem and in the context of the *Viagra* decision of Judge Magnuson, all three courts allowed animal studies to be used in those contexts, and so should they here.

Now, I hope I haven't stolen too much of Mr. Binstock's thunder, but I will turn it over to him, and he can now run his slide presentation because I know he has got more than that, but I think he will talk about some of the details.

THE COURT: I'm sure Mr. Binstock has some thunder left here.

MR. BINSTOCK: Okay. This is our response, of course, to the motion to exclude Dr. Smith. Previously indicated, Your Honor, Martyn Smith is a PhD. He is a professor of toxicology at the University of Berkeley; PhD in biochemistry; medical school, St. Bartholomew's Hospital, London.

He is a full member of the Society of Toxicology, actively involved in toxicological research funded by the

National Institute of Health. He serves on several boards of several peer reviewed journals and publishes extensively, and he has devoted his professional career to the study of toxic effects of chemicals and drugs in the human body at a cellular level.

Most importantly, the defendants have not in any way, shape or form challenged his credentials in toxicology. As Mr. Goldser has indicated, Dr. Smith in this case has compared and contrasts the toxicological profiles of Levaquin, levofloxacin, and Floxin and has come up with a conclusion of their similarities.

Specifically, Dr. Smith has concluded in his report that the similar pharmacokinetics, toxicology profile and mechanism of action of levofloxacin and ofloxacin indicate that they can be considered one and the same for toxicological purposes and that the epidemiological observations for ofloxacin are pertinent to levofloxacin as well.

That is important, and we'll talk about that in a minute. There are epi studies by Van der Linden dealing with ofloxacin that clearly show that ofloxacin is more tendon toxic than the other fluoroquinolones by far, especially in the elderly and those taking concomitant steroids.

As we have discussed and Ron has pointed out,

that is clear that the ofloxacin/floxacin situation, the racemate, the mirror image, the fact that the, J & J presented information to the FDA when they did the NDA saying that they are one and the same for many purposes, the FDA making that finding, these are very similar drugs, and they are tendon toxic in the same degree.

And that is why it is important that they be considered the same because there is vast epidemiological evidence about the severe tendon toxicity of floxacin, which as we have indicated is the precursor to Levaquin or levofloxacin.

Dr. Smith's testimony is admissible because the testimony is based upon sufficient facts or data, both through the *Daubert* test and Rule 707. His testimony is the product of reliable principles and methods, and this witness has applied the principles and methodologies reliably to the facts of this case.

Specifically, Dr. Smith in this case has supported every premise leading to his conclusion with studies from peer reviewed scientific literature. As the Court knows, you know, in the Reference Manual on Scientific Evidence, peer review is one of the most sacred pillars of scientific evidence.

Additionally, a pertinent consideration is whether the theory or technique has been subject to peer

reviewed publication. The study is relied upon by Dr. Smith. That was citing *Daubert*, in fact are peer reviewed. As pointed out already, there is no human study that has been conducted directly comparing the toxicity of Levaquin to Floxin.

Why? Because you can't do it because it would be harm to humans. In the absence of human data, Dr. Smith relied on the most relevant and valid in vitro and in vivo studies available. As already discussed and is referenced in the Manual of Scientific Evidence, it's unethical often to experiment on humans by exposing them to known doses of chemical agents.

Animal toxicological evidence often provides the best evidence, information about the risk of a disease from a chemical exposure. I am again referring the Court to the Reference Manual on Scientific Evidence 2000.

Additionally, Dr. Smith has relied on over 40 peer reviewed scientific studies, including human epidemiological studies, medical case reports, in addition to in vitro and in vivo studies, and clearly, Your Honor, we would say that that satisfies the sufficient data requirement of Rule 702.

THE COURT: If Dr. Smith were relying solely on animal studies, would his testimony be excludable?

MR. BINSTOCK: I think that would go to the

weight of the evidence versus the evidence being excluded on a *Daubert* situation, Your Honor. The toxicological research included or includes exposing animals to chemicals or drugs in vivo. These are some of the things that -- there is the Reference Manual on Scientific Evidence recognizes as valid research in the toxicological field.

And, of course, that's important because Dr. Smith looked at in vivo studies. Exposing animal cells or tissues, including those from humans, to chemicals or drugs in vitro, same there. Case reports that monitor human patients with documented chemical or drug exposure case studies, which was also part of his analysis in comparing levofloxacin and ofloxacin.

Your Honor, Dr. Smith's reliance on all three types of accepted toxicological evidence we believe satisfies reliable principles and methods required of Rule 702. Specifically, the reliability of Dr. Smith's application of the principles and methods of toxicology flows from, one, his careful explanations of how each study supports the premise for which it is offered.

Two, the rationality and understanding of his explanations. Three, the lack of analytical gaps. Four, defendants' total failure to identify any study that fails to support Dr. Smith's conclusions. The reliability of Dr. Smith's methodology is further supported by defendants'

own new drug application which utilized the same types of data and arrived at the same conclusion as did Dr. Smith.

This is a statement from the NDA. Data from nonclinical pharmacology and toxicology studies indicate that levofloxacin has a comparable safety profile to its racemate ofloxacin.

Overall conclusions: Data from nonclinical pharmacology, toxicology, absorption, distribution, metabolism and excretion studies provide sufficient information to support the safety of the proposed maximum dose of 500 milligrams.

The data from these nonclinical studies indicate for the most part administration of levofloxacin presents a comparable profile to its racemate ofloxacin. Your Honor, we would submit that the only criticism then defendants raise to this reliability of Dr. Smith's methodology is his reliance on animal studies, which as we discussed, animal studies and the reliance on animal studies usually, at least as I have seen it, and the courts have discussed it, goes to the weight of the evidence.

There is some courts that say that it can be brought up on cross-examination, but it doesn't go to the depths of an exclusion under *Daubert*. In fact, Dr. Rodricks, defendants' own toxicology expert, relies heavily on animal studies, many of which were the same as

those relied on by Dr. Smith. Dr. Rodricks's evaluation of the studies are common to both experts and did not contradict those of Dr. Smith.

Clearly, Your Honor, by failing to identify any study that did not support the proposition for which it was offered, defendants' wholesale condemnation of Dr. Smith's reliance on animal studies must fail, citing *General Electric*. We would submit that Dr. Smith's testimony is admissible entirely pursuant to Rule 702 of the Federal Rules of Evidence.

I think Ron has already brought out the fact that there is three cases that deal with animal studies, all of which are from this district that indicate that, again, it is a weight of the evidence type issue, not an exclusion type issue when relying on animal studies.

That's all I have, Your Honor.

THE COURT: Go ahead.

MR. GOLDSER: If I may make one more comment, Your Honor, the other thing to answer the last question that you asked about whether what if Dr. Smith is relying only on animal studies. I am not sure if I have this here. There it is. 21 C.F.R. 201.56 in the version that existed as of 2006 says that you can include evidence from animal studies alone in the label.

You can see it's highlighted. Conclusions based

on animal data but necessary for safe and effective use of the drug in humans shall be identified as such and included with human data in the appropriate section of the labeling.

So to the extent that either Dr. Smith or Dr. Zizic is relying on animal data alone, which of course they're not, they're still entitled to talk about what that animal data shows because it's available for use in the label. The regulations say so.

THE COURT: Isn't there case law that casts some doubt on animal studies alone?

MR. GOLDSER: There is. The three cases that we have cited, yours, Judge Schiltz's and Judge Magnuson's, all rely on a U. S. Supreme Court case called *GE* that I think Mr. Binstock just mentioned, and it talks about that.

None of those cases have referenced this regulation. None of them talked about where animal data shows up in labels, and so at the very least, they are all distinguishable on that basis. I don't think this regulation was ever presented to any of those courts.

THE COURT: Thank you, Mr. Goldser.

Mr. Dames, did you have anything else to add?

MR. DAMES: Just a few concluding remarks, Your Honor. I don't think I heard any contradiction of what I told the Court concerning the state of the medical literature and the scientific research on comparative

tendon toxicity between levofloxacin, ciprofloxacin and for that matter -- levofloxacin. If I understand the argument correctly, and it is dangerous to try to articulate somebody else's argument, but I'll plow ahead.

There is a comparison made between the chemical structures of ofloxacin and levofloxacin to suggest that some of Van der Linden's studies which purport to find a higher risk to ofloxacin can be extrapolated to levofloxacin. It confuses me because the simplest way to come at a conclusion as to what are the relative toxicities of compounds are to say, they have been studied in animals, and we know from the animal work there is this relative toxicity.

They have been studied in humans to add to the knowledge, and we know from humans when we do a direct test showing relative toxicities, this is the result. They have been studied in human tendon cells, and there are differences in the toxicities, and we know the results. All of that is lacking. It is an inference upon an inference, and they don't use any direct measurements either from animal work, any direct measurements from human work or any head-to-head measurements, now, in human tendon cells.

We have come a long way on the inferences that have been built upon inferences to get to this day in

court, and I think it proper now to finally suggest that scientific direct evidence, even taking the articles and the literature used and relied upon by their own experts, not only fail to support them, contradict the conclusions they seek to have come out of the mouths of their experts when we come to trial in this case.

Thank you, Your Honor.

THE COURT: Okay. Very well. Thank you.

What is next?

MR. GOLDSER: Dr. Holmes, that's our motion, and Mr. Fitzgerald will argue that one.

THE COURT: Okay. We've got about 17 minutes. Can we do it?

MR. DAMES: We still have Zizic to go specifically, but --

THE COURT: Okay.

MR. DAMES: If we were going to come back for Dr. Waymack on another day --

THE COURT: Waymack and Holmes, right?

MR. DAMES: Waymack and Holmes would probably be appropriate to come back another day, Your Honor.

THE COURT: And do we need to address Dr. Zizic more?

MR. DAMES: I was just going to make a couple of comments, and it's very brief on this one, Your Honor. I

did not, and I should have referred to this. One of the concerns that the courts have exhibited in *Daubert* are the litigation created opinions, and I just want to suggest that both Dr. Smith, and very specifically we have inquired into with Dr. Zizic, these were individuals whose experience with tendon toxicity and Levaquin started with this litigation.

And Dr. Zizic, for example, spent hundreds of hours in reviewing the literature and preparing his opinion after his retention. I think that is a fact that has to weigh heavily in the analysis of the sufficiency of any opinion that might be rendered concerning relative tendon toxicities.

It is a huge investment in an expert who for the first time is seeking to answer the questions posed by plaintiffs' counsel.

THE COURT: Mr. Goldser?

MR. GOLDSER: At the risk of repeating myself, I will repeat myself. Much of the evidence about the comparison between Floxin and Levaquin comes out of the NDA. Mr. Binstock showed you two examples. There are many, many more where Johnson & Johnson told the FDA, these two drugs are very similar in their safety profile, in their toxicology and in their pharmacology.

It doesn't take a whole lot to get from their

admissions to a conclusion that their opinions are admissible from Johnson & Johnson's admissions to the conclusion that our experts' opinions are admissible.

Nevertheless, both of them did extensive scientific research to the level required of professionals in their field, unlike that of Dr. Waymack who we will criticize on probably October 21st when we come back for Dr. Blume.

There is no question that Smith and Zizic have done a more than adequate job of reviewing the literature. Oh, my God, the volumes of the articles that I got from both of them is enormous that they have looked at, all of which have been presented to the defendants, of course.

So their work is impeccable, but it boils down to a few nubs, one of the most important is which, defendant admits it. Thank you.

THE COURT: Anything else, Mr. Dames? Okay. Very well.

So shall we stop today and then return for Waymack, Holmes, which I think are the only ones left, and then of course we have Blume at the appropriate time?

MR. GOLDSER: Might I convince the Court to take Holmes today? Waymack and Blume are the opposite side of each other's coin, and we might do them both together on October 21st.

THE COURT: Okay.

MR. DAMES: I would rather not, Your Honor, if we're going to try to shorten it up a little bit. I mean, I don't know that -- I don't know the reason why we need to compress it today if we're going to come back.

THE COURT: Okay. Mr. Goldser?

MR. GOLDSER: You will remember that Mr. Dames wanted to shorten up the time to get Dr. Holmes done so we could get him done. We are about to face a request for an IME which we are going to oppose. There are lots of things going with Dr. Holmes, and I think it's important that we get to him.

We said we have got twelve more minutes, if I might take advantage of it.

MR. DAMES: I sort of sense a contradiction there. There is a lot of stuff with Holmes and then the twelve minutes.

MR. GOLDSER: There are a lot of the issues that will come together because of the Court's ruling on it.

THE COURT: Let's look at the calendar and see when we can come back here. Blume is not going to be ready until when? Is that, did we set a time for that? 21st?

MR. ROBINSON: 21st of October, Your Honor.

THE COURT: Okay. Is there a convenient time next week or not?

MR. DAMES: I thought we had the 14th set for a hearing on the IME.

MS. VAN STEENBURGH: We have tentatively talked about that with Holly. We were going to do it as a telephonic hearing.

THE COURT: Yeah. That was going to be by telephone.

MS. VAN STEENBURGH: I don't -- so that was -- that's fine. Don't you have trial?

THE COURT: I have a trial every free day until we start this trial.

MR. DAMES: I can be here the 14th.

THE COURT: We probably could do that. I have a conflict in the morning. I have trial set in the afternoon, but we could do, we could probably do the end of the afternoon pretty easily at 4:30 and however long it takes because I don't have anything until I have to leave about 7:30.

MR. DAMES: We could combine the IME hearing.

MR. SAUL: What would that hearing be on the 14th?

THE COURT: The 14th would be on the remaining motions, which would be Waymack and Holmes. The others I think you indicated you were going to submit on the papers, and then the independent medical examination question that

is being raised.

MR. GOLDSER: We would do those in person as opposed to on the telephone?

THE COURT: In person, yes.

MR. ROBINSON: Your Honor, could I please be excused on the 14th? I'm not involved in those hearings, and I have other commitments that day.

THE COURT: That's fine, Mr. Robinson. We'll miss you, but that's okay. We expect you will be around the following month quite a bit.

MR. ROBINSON: Absolutely.

MR. DAMES: John Winter cannot be here the 14th for Waymack, but I thought we would do the Holmes, the combined IME and the *Daubert* motion on the 14th and do Waymack and Blume together?

THE COURT: Well, we could. I mean, we've got Blume the following week, right?

MR. ROBINSON: 21st, Your Honor.

THE COURT: Yeah. We could do that.

MR. DAMES: Okay.

THE COURT: If that works. Okay. Let's do that.

Yes, Mr. Saul?

MR. SAUL: And, Your Honor, we will be, we have a meet and confer on a very pressing discovery issue that we will be filing within a few days, and we would like to have

that heard at the same time that Dr. Holmes's motion is heard or the IME is heard.

THE COURT: We could do that unless you resolve it in the meet and confer.

MR. ROBINSON: That's a problem, Your Honor.

THE COURT: That's you?

MR. ROBINSON: That's me.

THE COURT: Okay. Well, we can do it on the 21st, then. We will set the time available then.

MS. VAN STEENBURGH: So what time on the 14th?

THE COURT: 4:30, and then the 21st, have we set a time yet?

MR. ROBINSON: 12:30, Your Honor.

THE COURT: 12:30. Okay. I think we've got it straight. Okay. The motions that we have heard today the Court will take under advisement and will issue a written order, other than the first one which the Court ruled on from the bench.

So thank you for the arguments today.

MR. DAMES: Thank you, Your Honor.

MR. GOLDSER: Thank you, Your Honor.

THE CLERK: All rise.

* * *

I, Kristine Mousseau, certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

Certified by: s/ Kristine Mousseau, CRR-RPR
Kristine Mousseau, CRR-RPR